Chronicle: results of a randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (XELOX) versus control

R. Glynne-Jones¹*, N. Counsell², P. Quirke³, N. Mortensen⁴, A. Maraveyas⁵, H. M. Meadows², J. Ledermann² & D. Sebag-Montefiore³

¹Department of Medical Oncology, Mount Vernon Centre for Cancer Treatment, London; ²CRUK & UCL Cancer Trials Centre, London; ³Leeds Institute of Molecular Medicine, University of Leeds, Leeds; ⁴Department of Colorectal Surgery, University of Oxford, Oxford; ⁵Queen’s Centre for Oncology and Haematology, Castle Hill Hospital, Hull, UK

Background: In stage III colon cancer, oxaliplatin/5-fluorouracil (5-FU)-based adjuvant chemotherapy (FOLFOX) improves disease-free survival (DFS) and overall survival (OS). In rectal adenocarcinoma following neoadjuvant chemoradiation (CRT), we examined the benefit of postoperative adjuvant capecitabine and oxaliplatin (XELOX) chemotherapy.

Methods: Eligible patients were randomly assigned following fluoropyrimidine-based CRT and curative resection to observation or six cycles of XELOX. The primary end point was DFS; secondary end points were acute toxicity and OS. 390 patients were required in each arm, to detect an improvement in 3-year DFS from 40% to 50.5%, with 85% power and two-sided 5% significance level.

Results: The study closed prematurely in 2008 because of poor accrual. Only 113 patients were randomly assigned to either observation (n = 59) or XELOX (n = 54). Compliance was poor, 93% allocated chemotherapy started and 48% completed six cycles. Protocolised dose reductions in XELOX were 39%, and levels of G3/G4 toxicity 40%. After a median follow-up of 44.8 months, 16 patients (27%) in the observation arm had relapsed or died compared with 12 patients (22%) in XELOX. The 3-year DFS rate was 78% with XELOX and 71% with observation [hazard ratio (HR) for DFS = 0.80; 95% confidence interval (CI) 0.38–1.69; P = 0.56]. The 3-year OS for XELOX and observation were 89% and 88%, respectively (HR for OS = 1.18; 95% CI 0.43–3.26; P = 0.75).

Conclusions: The observed improvement in DFS for adjuvant XELOX and similar OS were not statistically significant, as expected given the small number of patients and consequent low power. Our findings support the need for trials that test the role of neoadjuvant chemotherapy.

ClinicalTrials.gov Identifier: NCT00427713.

Key words: rectal adenocarcinoma, preoperative chemoradiation, metastatic disease, adjuvant chemotherapy, capecitabine, oxaliplatin

introduction

Postoperative 5-fluorouracil (5-FU)-based adjuvant chemotherapy improves overall survival (OS) in stage III colon cancer [1]. Oxaliplatin added to 5-FU-based chemotherapy improves disease-free survival (DFS) and OS [2, 3], and is considered an international standard for stage III colon cancer.

Locally advanced rectal cancer (LARC) has a high risk of local and distant recurrence. Many oncologists, and the European and National Comprehensive Cancer Network Guidelines, recommend a FOLFOX regimen as postoperative chemotherapy in patients with stage III or adverse histology following chemoradiation (CRT) and surgery [4–9]. The validity of this strategy has been questioned [10]. Trials that directly examined adjuvant 5-FU alone after CRT, have provided no evidence for its efficacy [11–13].

The Chronicle trial aimed to evaluate postoperative adjuvant chemotherapy following neoadjuvant chemoradiation (NCRT) in LARC. The trial examined whether six cycles of capecitabine...
and oxaliplatin (XELOX) over 4 months would improve DFS and OS compared with surgical follow-up alone. We report the results of acute toxicity and compliance in addition to DFS and OS.

patients and methods

The Chronicle trial was approved by institutional ethics committees of participating centres and monitored by an Independent Data Monitoring (IDMC) and Trial Steering Committee. Six-monthly review of recruitment was prospectively defined to assess the feasibility of obtaining a clinically worthwhile result, if accrual was lower than anticipated.

eligibility

Eligible patients were aged >18 years, with histologically confirmed rectal adenocarcinoma, located ≤15 cm from the anal verge, or below the peritoneal reflection. Surgery was carried out before randomisation, to start chemotherapy within 12 weeks of surgery. Before enrolment patients received preoperative fluoropyrimidine-based CRT, minimum total dose 45 Gy. Patients may have had up to a 12-week maximum of neoadjuvant fluoropyrimidine-based chemotherapy.

Other eligibility criteria included WHO performance status 0–1, adequate haematologic, renal, and hepatic function, complete resection of the primary tumour, a negative circumferential margin (CRM >1 mm), and no evidence of metastatic disease. Definitive histology at surgery required ypT0–T4, N0–N2.

Patients were excluded in the presence of metastatic disease (M1), R1 or R2 resections, and for significant cardiac disease, central nervous system disorders, known peripheral neuropathy, moderate/severe renal impairment, and pregnancy or lactation.

treatment

Patients were randomised to observation alone (Observation arm) or XELOX—capecitabine (1000 mg/m² orally twice daily days 1–14) and oxaliplatin (130 mg/m² day 1) as a 2-h infusion (XELOX arm) as indicated in the CONSORT diagram (Figure 1). A total of 6 3-weekly cycles were intended. Dose modifications for toxicity were defined in the protocol.

assessments

Pre-treatment evaluation included: computed tomography (CT) scans of chest, abdomen, and pelvis; demographic data, medical history, physical examination, ECG, carcino-embryonic antigen (CEA) determination; height, weight, vital signs, WHO performance status, haematology, and blood chemistry.

Adverse events were monitored during and for 28 days after study treatment. Toxicity was graded according to National Cancer Institute Common Toxicity Criteria, version 3.0. Neurotoxicity was monitored up to 3 years post-randomisation.

follow-up

Patients were evaluated clinically every 3 weeks following randomisation until 4 months, then 3-monthly until the end of the second year, 6-monthly until the end of the fifth year and then annually. Colonoscopy was recommended before surgery or within 3 months after surgery, and thereafter every third year. Abdo-pelvic CT scans or ultrasound and chest X-ray or thoracic CT were to be carried out at 6, 12, 18, 24, 36, and 48 months post-randomisation. CEA levels were measured every 3 months (starting 6 months post-randomisation) for the first 3 years and every 6 months thereafter. Assessments were made for local relapse, distant metastases, late toxicity, second cancers, and death. Patients were flagged at the UK Office of National Statistics to capture death notification.

statistical analysis

Patients were randomly assigned 1:1 between trial arms using permuted blocks, stratified by surgeon and pathological nodal status.

The primary end point was DFS, defined as the time from randomisation to relapse, development of a new cancer or death, whichever occurred first. Three hundred and ninety patients were required in each arm to detect an improvement in 3-year DFS from 40% to 50.5% [equivalent to a hazard ratio (HR) of 0.75], with 85% power and two-sided 5% significance level. With allowance for loss to follow-up, the target sample size was 800 patients in total, assuming an enrolment, and follow-up period of 3 years.

If an advantage was observed for postoperative chemotherapy, it was planned to explore whether it was consistent across various subgroups described in the statistical analysis plan. Secondary end points were OS, measured from date of randomisation until death from any cause, incidence rates of acute toxicity, and compliance to treatment.

![Figure 1. CONSORT diagram.](https://academic.oup.com/annonc/article-abstract/25/7/1356/2801207)
Hazard ratios with 95% confidence intervals (CIs) were calculated using the Cox proportional hazards model. Survival curves are presented using the Kaplan–Meier method. Patients were censored using the date they were last seen if no event had occurred. Analysis was carried out on an intention-to-treat basis, unless otherwise specified, and generated using SAS software version 9.3, (SAS Institute, Cary NC).

results

accrual

Between 2004 and 2008, 113 patients were randomised; Table 1 shows the baseline characteristics. After 4 years of slower-than-anticipated accrual, the trial was terminated early on the recommendation of the IDMC.

compliance

Fifty-four patients were randomly assigned to XELOX and 59 to the observation arm. At least one cycle of study treatment was received by 50 patients (92.6%). The planned six cycles of chemotherapy were received by only 26 (48.1%). Twenty-one (38.9%) had a dose reduction and 21 (38.9%) had a dose delay, Table 2.

Median total oxaliplatin dose received was 601 mg/m², compared with a per-protocol six-cycle dose of 780 mg/m². Median total capecitabine dose received was 96 923 mg/m², compared with a per-protocol six-cycle dose of 168 000 mg/m².

Therapy after relapse was received by 9 (16.7%) XELOX and 15 (25.4%) patients in the observation arm. After relapse, in the XELOX and observation arms, respectively, 6 (11.1%) and 7 (11.9%) patients received chemotherapy, 4 (7.4%) and 7 (11.9%) received surgery, 2 (3.7%) and 2 (3.4%) received palliative care, 1 (1.9%) and 1 (1.7%) received radiotherapy, and 1 (1.9%) XELOX patient was offered a different trial.

toxicity

Fifty (92.6%) XELOX patients received at least one cycle of treatment—defined as the safety population. Twenty (40.0%) of the

| Table 1. Baseline characteristics—intention-to-treat population |
|-----------------|-----------------|
| Variables       | Follow-up only (N = 59) | Capecitabine + Oxaliplatin (N = 54) |
| Age at random assignment (years) | Median (IQR) | Median (IQR) |
| Time from chemotherapy to surgery (weeks) | 9.2 (7.4–11.4) | 8.7 (7.1–11.7) |
| Time from radiotherapy to surgery (weeks) | 8.9 (7.1–10.6) | 8.5 (7.1–11.9) |
| Time from surgery to randomisation (weeks) | 8.7 (7.3–10.6) | 8.9 (7.0–10.6) |
| Gender |  |
| Female | 20 (33.9) | 10 (18.5) |
| Male | 39 (66.1) | 44 (81.5) |
| WHO performance status |  |
| 0 | 37 (62.7) | 33 (61.1) |
| 1 | 22 (37.3) | 21 (38.9) |
| Tumour site |  |
| Lower (0–4.9 cm) | 30 (50.9) | 25 (46.3) |
| Middle (5–9.9 cm) | 16 (27.1) | 17 (31.5) |
| Upper (10–15 cm) | 13 (22.0) | 12 (22.2) |
| Tumour stage (ypT) |  |
| T0 | 1 (1.7) | 8 (14.8) |
| T1 | 2 (3.4) | 2 (3.7) |
| T2 | 14 (23.7) | 15 (27.8) |
| T3 | 38 (64.4) | 27 (50.0) |
| T4 | 4 (6.8) | 2 (3.7) |
| Nodal status (ypN) |  |
| N0 | 31 (52.4) | 44 (81.5) |
| N1 | 23 (39.0) | 7 (13.0) |
| N2 | 5 (8.5) | 3 (5.6) |
| Surgical technique |  |
| Abdomino-perineal resection | 21 (36.2) | 25 (47.2) |
| Anterior resection | 31 (53.4) | 27 (50.9) |
| Low Hartmann’s | 3 (5.2) | 0 (0.0) |
| Other | 3 (5.2) | 1 (1.9) |
| Missing | 1 | 1 |

Note: the apparent imbalance for some of the baseline characteristics (e.g., gender) is due to chance: patients were randomly assigned by blocked stratification using nodal status and surgeon, but with 82 surgeons there were many randomisation ‘cells’, and with only 113 recruited patients out of the target of 800, this method of randomisation can produce chance imbalances.
safe population) reported grade 3 or higher toxicity, Table 3. Three (6.0%) reported a grade 4 toxicity [sensory neuropathy (n = 2) and diarrhoea (n = 1)]. There was one treatment-related death from diarrhoea.

Nine patients reported a grade 3/4 adverse event during follow-up. Six XELOX patients reported 8 late toxicities: bowel obstruction (G4, n = 1), malignant fistula (G4, n = 1), neuropathy (G3, n = 2), impaired bladder function (G3, n = 1), pulmonary embolism (G3, n = 1), pain (G3, n = 1), and blepharospasm (G3, n = 1). Three patients in the observation arm reported three late toxicities: angina (G3, n = 1), back pain (G3, n = 1), and poor bowel control (G3, n = 1).

### efficacy

The median follow-up was 44.8 months, censoring those who had died. Only two local recurrences have been observed. There were 16 (27.2%) observation and 12 (22.2%) XELOX patients who had relapsed or died (supplementary Table S1, available at Annals of Oncology online), with 3-year DFS of 71.3% and 77.5%, respectively. The HR for DFS was 0.80 (95% CI 0.38–1.69; P = 0.56), in favour of XELOX (Figure 2A). The observed 3-year DFS rates were higher than expected (40%–50% from the sample size calculation), and the HR was close to the target value of 0.75. The HR after adjusting for factors that are imbalanced in Table 1 was 0.84 (95% CI 0.37–1.93; P = 0.69).

Fifteen patients died, 7 observation [11.9%; rectal cancer (n = 6), rectal and breast cancer with brain metastases (n = 1)] and 8 XELOX [14.8%; rectal cancer (n = 6), chemotherapy-related (n = 1), pharyngeal tumour (n = 1)], with 3-year OS of 87.8% and 88.8%, respectively. The HR for OS was 1.18 (95% CI 0.43–3.26; P = 0.75) in favour of observation only (Figure 2B). The HR after adjusting for factors that appear imbalanced in Table 1 was 1.42 (95% CI 0.44–4.52; P = 0.55).

### discussion

The Chronicle trial is unique in comparing XELOX postoperatively against observation alone in LARC treated with preoperative CRT. Results show that after a median follow-up of 44.8 months, the 3-year DFS rate was 78% with XELOX and 71% with observation (HR for DFS 0.80; 95% CI 0.38–1.69; P = 0.56). Hence, no statistically significant benefit of adjuvant XELOX chemotherapy was found, but the study was underpowered with only 113 patients reducing the planned power of 85% to <20% for the primary end point.

We did not specify baseline clinical stage as an eligibility criterion; following the CR07 trial, most patients in the UK with resectable LARC received short-course preoperative radiotherapy (5 × 5 Gy). Chemoradiation tended to be given for fixed or unresectable cancers.

Based on results of a meta-analysis in colon cancer [14], it is assumed chemotherapy should start as soon as possible following surgery, and not be delayed beyond 3 months. In the Chronicle study, the median time from surgery to randomisation was 8 weeks. Compliance to postoperative chemotherapy was poor. Only 26 patients (48.1%) received the planned six cycles. This finding is consistent with other studies.

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**Table 2. Compliance to chemotherapy—intention-to-treat population**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cycles</th>
<th>Capecitabine + Oxaliplatin (N = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cycles received</td>
<td>0</td>
<td>3 (5.6)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>12 (22.2)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3 (5.6)</td>
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<td>3</td>
<td>2 (3.7)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>5 (9.3)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2 (3.7)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>26 (48.1)</td>
</tr>
<tr>
<td>Dose delay</td>
<td>1</td>
<td>6 (11.1)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>(1.9)</td>
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<tr>
<td></td>
<td>3</td>
<td>6 (11.1)</td>
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<td></td>
<td>4</td>
<td>9 (16.7)</td>
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<tr>
<td></td>
<td>6</td>
<td>4 (7.4)</td>
</tr>
<tr>
<td>Any dose delay</td>
<td>21 (38.9)</td>
<td></td>
</tr>
<tr>
<td>Dose reduction</td>
<td>1</td>
<td>8 (14.8)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3 (5.6)</td>
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<td>2 (3.7)</td>
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<tr>
<td></td>
<td>4</td>
<td>6 (11.1)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>4 (7.4)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Any dose reduction</td>
<td>21 (38.9)</td>
<td></td>
</tr>
<tr>
<td>Total dose Capecitabine given (mg/m²)</td>
<td>Median (IQR)</td>
<td>96.923 (28.290, 160.000)</td>
</tr>
<tr>
<td>Total dose Oxaliplatin given (mg/m²)</td>
<td>601 (130.769)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3. Reported grade 3 or 4 toxicities—safety population**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Capecitabine + Oxaliplatin (N = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any toxicity (each patient counted once)</td>
<td>20 (40.0)*</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>8 (16.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (12.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (8.0)</td>
</tr>
<tr>
<td>Neuropathy:sensory</td>
<td>4 (8.0)</td>
</tr>
<tr>
<td>Hand–Foot reaction</td>
<td>3 (6.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (6.0)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Clumsiness</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Granulocytes</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Pain–abdomen</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Paraesthesia/dysesthesia</td>
<td>1 (2.0)</td>
</tr>
</tbody>
</table>

*Grade 4 = 3 patients (6.0%): diarrhoea (n = 1), neuropathy:sensory (n = 2).
The Chronicle trial benefits from high levels of complete data, pathologic verification, and mature follow-up of individuals within the trial. Yet few patients were actually accrued from a large number of recruiting centres, which meant that patients receiving XELOX were not well matched for individual prognostic factors versus those in the observation arm. In particular, the two study groups differed slightly in the number of patients achieving a pathological complete response, because patients were randomly assigned using blocked stratification by nodal status and surgeon (82 surgeons, for only 113 of 800 patients). However, outcomes are similar even after adjusting for these differences.

By restricting eligibility to patients with a CRM >1 mm, we selected patients with more favourable outcomes because non-responders to CRT were effectively excluded. This factor might explain the paucity of relevant events such as low local recurrence rate.

*Figure 2.* (A) Disease-free and (B) overall survival curves according to treatment arms in all patients—intention-to-treat population.
The evidence-base for postoperative adjuvant chemotherapy in LARC is scanty. A phase III Japanese trial of oral UFT [15] in 274 patients, suggests an advantage to postoperative adjuvant chemotherapy in rectal cancer although no NCRT was given and surgery involved bilateral lateral pelvic lymph node dissection. A recent meta-analysis [16] of 21 randomised, controlled trials in 9221 patients, examined postoperative chemotherapy and showed a significant benefit in terms of DFS (HR = 0.75, 95% CI 0.68–0.83) and OS (HR = 0.83, 95% CI 0.76–0.91) for patients with rectal cancer administered postoperative fluoropyrimidine-based chemotherapy (without oxaliplatin) when compared with observation alone. However, only three studies [11, 17, 18] included patients who had received preoperative radiotherapy. In the largest EORTC 22 921 study [11, 19] in 1011 patients with T3/T4 resectable, there was no significant benefit in terms of DFS or OS from the addition of postoperative 5-fluorouracil and folinic acid.

A Korean study randomised 320 patients (161 to 5-FU, 159 to FOLFOX) with ypstage II and III rectal cancer following CRT [20]. After a median follow-up of 22.5 months, estimated 2-year DFS rate was 82.0% in FOLFOX and 69.4% in the 5-FU arm (HR = 0.46; 95% CI 0.28–0.76; \( P = 0.002 \)).

There is a well-recognised problem of delivery and compliance to chemotherapy following preoperative CRT and surgery, because of slow recovery and healing, poor tolerance, marked dose reductions, and patient reluctance—requiring at least 40% of patients [10, 11, 21]. The Chronicle trial demonstrates only 48% of patients allocated chemotherapy completed six cycles.

In contrast, compliance to chemotherapy in the preoperative setting is high [22] and delivered more easily than postoperative [23], enabling full systemic doses of chemotherapy to be delivered at an early stage rather than a delay of up to 18 weeks associated with CRT.

unpublished studies

The Eastern Cooperative Oncology Group (E3201) trial closed after 225 patients of the planned 3150 had been enrolled, when the GI Intergroup developed an alternative trial with bevacizumab (E5204). An updated analysis [24] showed no difference in OS between patients who received 5-FU alone, oxaliplatin-based or irinotecan-based adjuvant chemotherapy. The follow-on E5204 trial aimed to randomise 2100 patients between modified FOLFOX 6 with or without bevacizumab but closed in 2009.

The PETACC 6 (1094 patients) [25] and the German ARO/CAO/AIO-04 trials (1259 patients) [26] may provide further evidence regarding the role of postoperative FOLFOX (ARO/CAO/AIO-04) or XELOX (PETACC 6) versus adjuvant 5-FU/capecitabine alone.

The Dutch CKTO/2003-16/PROCTOR/SCRIPT study initially randomised patients after short-course preoperative radiotherapy (5 × 5 Gy) to capecitabine or control, but was amended to include preoperative CRT. Preliminary results in 470 of the 840 originally intended patients, show the 3-year DFS was 67.4% for chemotheraphy versus 66.1% for observation (HR 0.835, 95% CI 0.61–1.13; \( P = 0.24 \)) [27].

In Chronicle, there were sufficient centres open, but the high rate of refusals to take part reflects lack of equipoise on the part of oncologists and strong preferences by patients for no further treatment following CRT. This is a well-recognised problem in non-blinded randomised trials and is unlikely to be due to a specific feature of rectal cancer.

conclusion

The Chronicle trial did not detect a significant difference in DFS or OS for adjuvant XELOX. No definitive conclusion can be drawn from a trial with inadequate numbers, poor compliance and insufficient statistical power. We remain unsure of the advantage of additional adjuvant chemotherapy following CRT, either in terms of 5-FU alone or combined with oxaliplatin, and of specific subgroups who might benefit most/least. Although unable to provide a definitive result, this trial in terms of the HR of 0.80 for DFS (95% CI 0.38–1.69), can contribute to future reviews and meta-analyses.

The poor compliance to oxaliplatin containing chemotherapy in the postoperative setting following CRT therefore supports the hypothesis that noadjuvant chemotherapy—as piloted in the UK BACCHUS Study (NCT01650428) and the US NCCTG N1048 PROSPECT trial (NCT01515787)—might prove a more effective strategy.

acknowledgements

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funding

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disclosure

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